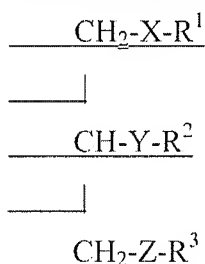


AMENDMENTS TO THE CLAIMS

1. (Currently Amended) A ~~lipid-based~~liposomal drug delivery system for administering an active ~~lysolipid-drug substance, which is not a substrate for lysophospholipase~~selected from lysolipid derivatives, wherein the active drug substance is present in the lipid-based system in the form of a prodrug, said prodrug being a lipid derivative having the following formula:



wherein

X and Z are O;

Y is -OC(O)-, Y being connected to R² via either the oxygen or carbonyl carbon atom;

R¹ and R² are each independently an alkyl group (CH₂)_nCH₃, where n is any one of 11-29; and,

R³ is a member selected from the group consisting of phosphatidic acid, phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl inositol, phosphatidyl glycerol, and phosphatidyl serine, said prodrug furthermore being a substrate for extracellular phospholipase A2 whereby R² can be hydrolytically cleaved off, whereas R² remains substantially unaffected, and whereby the active drug substance is liberated in the form of a lysolipid derivative which is not a substrate for lysophospholipase, said system further comprising lipopolymers or glycolipids so as to present hydrophilic chains on the surface of the system, to tissues expressing increased levels of extracellular phospholipase A2, comprising:

(a) A prodrug lipid derivative having:

- (1) An alkyl-linked aliphatic group of a length of at least 7 carbon atoms;
- (2) An acyl linked organic radical having at least 7 carbon atoms, and
- (3) A hydrophilic moiety, and

(b) At least one lipopolymer or glycolipid.

2. (Currently Amended) The drug delivery system according to claim 1, wherein the lipopolymers or glycolipids are represented by at least a fraction of the prodrug-lipid-derivative.

3. (Previously Presented) The drug delivery system according to claim 1, wherein the polymer of the lipopolymer is selected from the group consisting of polyethylene glycol, poly(lactic acid), poly(glycolic acid), poly(lactic acid)-poly(glycolic acid) copolymers, polyvinyl alcohol, polyvinylpyrrolidone, polymethoxazoline, polyethyloxazoline, polyhydroxypropyl methacrylamide, polymethacrylamide, polydimethylacrylamide, and derivatised celluloses.

4-8. (Cancelled)

9. (Currently Amended) The drug delivery system according to claim 1, wherein the prodrug lipid-derivative constitutes 15-100 mol% of the total dehydrated lipid-based system.

10. (Previously Presented) The drug delivery system according to claim 1, wherein the lipopolymer constitutes 1-50 mol% of the total dehydrated system.

11. (Cancelled)

12. (Previously Presented) The drug delivery system according to claim 1, which is in the form of liposomes wherein a second drug substance is incorporated.

13. (Previously Presented) A drug delivery system according to claim 12, wherein the second drug substance is a therapeutically and/or prophylactically active substance selected from the group consisting of (i) antitumor agents, (ii) antibiotics and antifungals, and (iii) antiinflammatory agents.

14. (Original) A pharmaceutical composition comprising the lipid-based drug delivery system according to claim 1 and optionally a pharmaceutically acceptable carrier.

15. (Currently amended) A method for selectively drug targeting to neoplastic cells within a mammal having an extracellular phospholipase A2 activity which is at least 25% higher compared to the normal activity in said areas, by administering to the mammal in need thereof an efficient amount of the ~~lipid-based~~ drug delivery system according to claim 1.

16. (Currently Amended) A method of treating a mammal by administering to the mammal in need thereof an efficient amount of the ~~lipid-based~~ drug delivery system according to claim 1.

17. (Previously Presented) The method according to claim 16 for the treatment of diseases or conditions associated with a localized increase in extracellular phospholipase A2 activity in mammalian tissue.

18. (Original) The method according to claim 17, wherein the diseases or conditions are selected from the group consisting of inflammatory conditions and cancer.

19. (Original) The method according to claim 18, wherein the type of cancer is selected from the group consisting of brain cancer, breast cancer, lung cancer, colon cancer, ovarian cancer, leukemia, lymphoma, sarcoma and carcinoma.

20. (Previously Presented) The method according to claim 15, wherein the increase in extracellular phospholipase A2 activity is at least 25% compared to the normal level of activity in the tissue in question.

21. (Currently Amended) A method according to claim 20, wherein the ~~lipid-based~~ drug delivery system becomes localized in a diseased tissue after administration and which, after

degradation by extracellular phospholipase A2, leads to an increase in membrane permeability of cells in the diseased tissue.

22. (Currently Amended) The method according to claim 20, wherein the ~~lipid-based~~ drug delivery system includes a second drug substance, a membrane component, and/or an auxiliary drug substance which acts as an proactivator for extracellular phospholipase A2.

23. (Currently Amended) The method according to claim 20, wherein the ~~lipid-based~~ drug delivery system becomes localized in a diseased tissue after administration, and wherein degradation of the ~~lipid-based~~ drug delivery system by extracellular phospholipase A2 in the diseased tissue is accelerated by a localized increase in temperature in said tissue.

24. (Original) The method according to claim 15 for the treatment of diseases or conditions selected from the group consisting of inflammatory conditions and cancer.

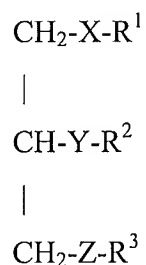
25. (Withdrawn) A lipid-based drug delivery system for administration of an second drug substance, wherein the second drug substance is incorporated in the system, said system including lipid derivatives which has (a) an aliphatic group of a length of at least 7 carbon atoms and an organic radical having at least 7 carbon atoms, and (b) a hydrophilic moiety, where the lipid derivative furthermore is a substrate for extracellular phospholipase A2 to the extent that the organic radical can be hydrolytically cleaved off, whereas the aliphatic group remains substantially unaffected, so as to result in an organic acid fragment or an organic alcohol fragment and a lysolipid fragment, said lysolipid fragment not being a substrate for lysophospholipase, said system having included therein lipopolymers or glycolipids so as to present hydrophilic chains on the surface of the system.

26. (Withdrawn) The drug delivery system according to claim 25, wherein the lipopolymers or glycolipids are represented by at least a fraction of the prodrug.

27. (Withdrawn) The drug delivery system according to claim 25, wherein the polymer of the lipopolymer is selected from the group consisting of polyethylene glycol, poly(lactic acid), poly(glycolic acid), poly(lactic acid)-poly(glycolic acid) copolymers, polyvinyl alcohol, polyvinylpyrrolidone, polymethoxazoline, polyethyloxazoline, polyhydroxypropyl methacrylamide, polymethacrylamide, polydimethylacrylamide, and derivatised celluloses.

28. (Withdrawn) The drug delivery system according to claim 25, wherein the organic radical which can be hydrolytically cleaved off, is an auxiliary drug substance or an efficiency modifier for the second drug substance.

29. (Withdrawn) The drug delivery system according to claim 25, wherein the lipid derivative is a lipid derivative of the following formula:



wherein

X and Z independently are selected from O, CH₂, NH, NMe, S, S(O), and S(O)₂;

Y is -OC(O)-, Y then being connected to R² via either the oxygen or carbonyl carbon atom;

R¹ is an aliphatic group of the formula Y¹Y²;

R² is an organic radical having at least 7 carbon atoms;

where Y^1 is $-(CH_2)_{n1}-(CH=CH)_{n2}-(CH_2)_{n3}-(CH=CH)_{n4}-(CH_2)_{n5}-(CH=CH)_{n6}-(CH_2)_{n7}-(CH=CH)_{n8}-(CH_2)_{n9}$, and the sum of $n1+2n2+n3+2n4+n5+2n6+n7+2n8+n9$ is an integer of from 9 to 29; $n1$ is zero or an integer of from 1 to 29, $n3$ is zero or an integer of from 1 to 20, $n5$ is zero or an integer of from 1 to 17, $n7$ is zero or an integer of from 1 to 14, and $n9$ is zero or an integer of from 1 to 11; and each of $n2$, $n4$, $n6$ and $n8$ is independently zero or 1; and Y^2 is CH_3 or CO_2H ; where each Y^1 - Y^2 independently may be substituted with halogen or C_{1-4} -alkyl,

R^3 is selected from phosphatidic acid (PO_2-OH), derivatives of phosphatidic acid and bioisosters to phosphatic acid and derivatives thereof.

30. (Withdrawn) The drug delivery system according to claim 29, wherein R^2 is an aliphatic group of a length of at least 7 carbon atoms.

31. (Withdrawn) The drug delivery system according to claim 30, wherein R^2 is a group of the formula Y^1Y^2 .

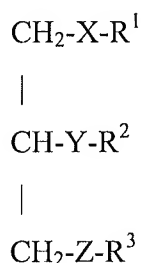
32. (Withdrawn) The drug delivery system according to claim 25, wherein at least a fraction of the prodrug is of the formula defined in claim 29, wherein R^3 is a derivative of phosphatidic acid to which a polymer selected from the group consisting of polyethylene glycol, poly(lactic acid), poly(glycolic acid), poly(lactic acid)-poly(glycolic acid) copolymers, polyvinyl alcohol, polyvinylpyrrolidone, polymethoxazoline, polyethyloxazoline, polyhydroxypropyl methacrylamide, polymethacrylamide, polydimethylacrylamide, and derivatized celluloses, is covalently attached.

33. (Withdrawn) The drug delivery system according to claim 25, wherein the lipid derivative constitutes 15-100 mol% of the total dehydrated system.

34. (Withdrawn) The drug delivery system according to claim 25, wherein the lipopolymer constitutes 1-50 mol% of the total dehydrated system.

35. (Withdrawn) The drug delivery system according to claim 25, wherein the system is in the form of liposomes.
36. (Withdrawn) The drug delivery system according to claim 25, wherein the second drug substance is a therapeutically and/or prophylactically active substance selected from (i) antitumor agents, (ii) antibiotics and antifungals, and (iii) antiinflammatory agents.
37. (Original, Withdrawn) A pharmaceutical composition comprising the drug delivery system according to claim 25 and optionally a pharmaceutically acceptable carrier.
38. (Withdrawn) A method for selectively drug targeting to neoplastic cells to areas within a mammalian body having a extracellular phospholipase A2 activity which is at least 25% higher compared to the normal activity in said areas, by administering to the mammal in need thereof an efficient amount of the drug delivery system defined in claim 25.
39. (Withdrawn) A method of treating a mammal by administering to the mammal in need thereof an efficient amount of the drug delivery system defined in claim 25.
40. (Withdrawn) The method according to claim 39 for the treatment of diseases or conditions associated with a localized increase in extracellular phospholipase A2 activity in mammalian tissue.
41. (Original, Withdrawn) The method according to claim 40, wherein the diseases or conditions are selected from the group consisting of inflammatory conditions and cancer.
42. (Original, Withdrawn) The method according to claim 41, wherein the type of cancer is selected from the group consisting of brain cancer, breast cancer, lung cancer, colon cancer, ovarian cancer, leukemia, lymphoma, sarcoma and carcinoma.

43. (Original, Withdrawn) The method according to claim 38, wherein the increase in extracellular phospholipase A2 activity is a least 25% compared to the normal level of activity in the tissue in question.
44. (Withdrawn) The method according to claim 43, wherein the drug delivery system becomes located in diseased tissue after administration and, after degradation by extracellular phospholipase A2, leads to an increase in membrane permeability of cells in the diseased tissue.
45. (Withdrawn) The method according to claim 43, wherein the drug delivery system includes a second drug substance, a membrane component, and/or an auxiliary drug substance which acts as an proactivator for extracellular phospholipase A2.
46. (Withdrawn) The method according to claim 43, wherein the drug delivery system becomes located in a diseased tissue after administration, and wherein degradation of the drug delivery system by extracellular phospholipase A2 in the diseased tissue is accelerated by a localized increase in temperature in said tissue.
47. (Withdrawn) The method according to claim 38, wherein the diseases or conditions are selected from the group consisting of inflammatory conditions and cancer.
48. (Withdrawn) A lipid derivative of the following formula:



wherein

X and Z independently are selected from O, CH₂, NH, NMe, S, S(O), and S(O)₂;

Y is -OC(O)-, Y then being connected to R² via either the oxygen or carbonyl carbon atom;

R¹ is an aliphatic group of the formula Y¹Y²;

R² is an organic radical having at least 7 carbon atoms;

where Y¹ is -(CH₂)_{n1}-(CH=CH)_{n2}-(CH₂)_{n3}-(CH=CH)_{n4}-(CH₂)_{n5}-(CH=CH)_{n6}-(CH₂)_{n7}-(CH=CH)_{n8}-(CH₂)_{n9}, and the sum of n1+2n2+n3+2n4+n5+2n6+n7+2n8+n9 is an integer of from 9 to 29; n1 is zero or an integer of from 1 to 29, n3 is zero or an integer of from 1 to 20, n5 is zero or an integer of from 1 to 17, n7 is zero or an integer of from 1 to 14, and n9 is zero or an integer of from 1 to 11; and each of n2, n4, n6 and n8 is independently zero or 1; and Y² is CH₃ or CO₂H; where each Y¹-Y² independently may be substituted with halogen or C₁₋₄-alkyl,

R³ is selected from derivatives of phosphatidic acid to which a hydrophilic polymer is attached.

49. (Withdrawn) The lipid derivative according to claim 48, wherein the hydrophilic polymer is selected from polyethylene glycol, poly(lactic acid), poly(glycolic acid), poly(lactic acid)-poly(glycolic acid) copolymers, polyvinyl alcohol, polyvinylpyrrolidone, polymethoxazoline, polyethyloxazoline, polyhydroxypropyl methacrylamide, polymethacrylamide, polydimethylacrylamide, and derivatized celluloses.

50. (Withdrawn) The lipid derivative according to claim 48, wherein X and Z are O.

51. (Withdrawn) The lipid derivative according to claim 48, wherein X and Z are O, R¹ and R² are independently selected from alkyl groups, (CH₂)_nCH₃, where n is 11, 12, 13, 14, 15, 16,

17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29; Y is -OC(O)-, Y then being connected to R² via the carbonyl carbon atom.

52. (Withdrawn) The pharmaceutical composition comprising the lipid derivative according to claim 48 and optionally a pharmaceutically acceptable carrier.

53. (Withdrawn) The pharmaceutical composition according to claim 52, wherein the lipid derivative is dispersed in the form of a liposome or a micelle.

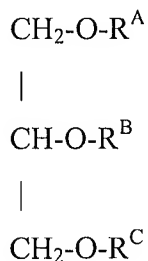
54. (Withdrawn) The method of treating a mammal by administering to the mammal in need thereof an efficient amount of the lipid derivative defined in claim 48.

55. (Withdrawn) The use according to claim 54, wherein the diseases or conditions are selected from the group consisting of inflammatory conditions, and cancer.

56. (Withdrawn) The use according to claim 55, wherein the type of cancer is selected from the group consisting of brain cancer, breast cancer, lung cancer, colon cancer, ovarian cancer, leukemia, lymphoma, sarcoma and carcinoma.

57. (Withdrawn) A lipid-based drug delivery system for administering an active lysolipid drug substance, which is not a substrate for lysophospholipase, to tissues expressing increased levels of extracellular phospholipase A2, comprising:

(a) a prodrug lipid derivative having the formula:



wherein R^A is an ether-linked fatty acid chain having at least 7 carbon atoms, R^B is an acyl-linked fatty acid chain having at least 7 carbon atoms and R^C is chosen from the group consisting of phosphatidic acid, phosphatidyl choline, phosphatidyl glycerol and phosphatidyl serine; and

(b) at least one lipopolymer or glycolipid.

58. (Withdrawn) The lipid based drug delivery system according to claim 57, wherein the lipopolymers or glycolipids are represented by at least a fraction of the prodrug lipid derivative.

59. (Withdrawn) The lipid-based drug delivery system according to claim 57, wherein the the polymer of the lipopolymer is selected from the group consisting of polyethylene glycol, poly(lactic acid), poly(glycolic acid), poly(lactic acid)-poly(glycolic acid) copolymers, polyvinyl alcohol, polyvinylpyrrolidone, polymethoxazoline, polyethyloxazoline, polyhydroxypropyl methacrylamide, polymethacrylamide, polydimethylacrylamide, and derivatized celluloses.

60. (Withdrawn) The lipid-based drug delivery system according to claim 57, wherein the lipid-based system is in the form of liposomes .

61. (Withdrawn) The lipid-based drug delivery system according to claim 57, which is in the form of liposomes wherein a second drug substance is incorporated.

62. (Withdrawn) The lipid-based drug delivery system according to claim 57, wherein the second drug substance is a therapeutically and/or prophylactically active substance selected from the group consisting of (i) antitumor agents, (ii) antibiotics and antifungals and (iii) anti-inflammatory agents.

63. (Withdrawn) A pharmaceutical composition comprising the lipid-based drug delivery system according to claim 57 and optionally a pharmaceutically acceptable carrier.

64. (Withdrawn) A method for selectively drug targeting to neoplastic cells within a mammalian body having a extracellular phospholipase A2 activity which is at least 25% higher compared to the normal activity in said areas, by administering to the mammal in need thereof an efficient amount of the lipid-based drug delivery system according to claim 57.

65. (Withdrawn) A method of treating a mammal by administering to the mammal in need thereof an effective amount of the lipid-based drug delivery system according to claim 57.

66. (Withdrawn) The method according to claim 64 for the treatment of diseases or conditions associated with a localized increase in extracellular phospholipase A2 activity in mammalian tissue.

67. (Withdrawn) The method according to claim 66, wherein the diseases or conditions are selected from the group consisting of inflammatory conditions and cancer.

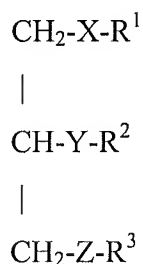
68. (Withdrawn) The method according to claim 67, wherein the type of cancer is selected from the group consisting of brain cancer, breast cancer, lung cancer, colon cancer, ovarian cancer, leukemia, lymphoma, sarcoma and carcinoma.

69. (Withdrawn) The method according to claim 64, wherein the increase in extracellular phospholipase A2 activity is a least 25% compared to the normal level of activity in the tissue in question.

70. (Withdrawn) The method according to any one of claims 15, 16, 38, 39, 54 or 65, wherein the mammal is a human.

71. (Withdrawn) A liposomal drug delivery system for administering an active lysolipid drug substance, which is not a substrate for lysophospholipase, to tissues expressing increased levels of extracellular phospholipase A2, comprising:

(a) a prodrug lipid derivative having the formula:



wherein

X and Z independently are selected from O, CH₂, NH, NMe, S, S(O), and S(O)₂;

Y is -OC(O)-, Y then being connected to R² via either the oxygen or carbonyl carbon atom;

R¹ is an aliphatic group of the formula Y¹Y²; where Y¹ is -(CH₂)_{n1}-(CH=CH)_{n2}-(CH₂)_{n3}-(CH=CH)_{n4}-(CH₂)_{n5}-(CH=CH)_{n6}-(CH₂)_{n7}-(CH=CH)_{n8}-(CH₂)_{n9}, and the sum of

n1+2n2+n3+2n4+n5+2n6+n7+2n8+n9 is an integer of from 9 to 29; n1 is zero or an integer of from 1 to 29, n3 is zero or an integer of from 1 to 20, n5 is zero or an integer of from 1 to 17, n7 is zero or an integer of from 1 to 14, and n9 is zero or an integer of from 1 to 11; and each of n2, n4, n6 and n8 is independently zero or 1; and Y² is CH₃ or CO₂H; where each Y¹-Y²

independently may be substituted with halogen or C₁₋₄-alkyl,

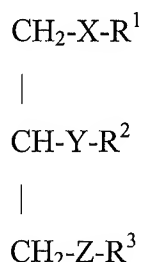
R² an alkyl group (CH₂)_nCH₃ where n is any one of 11-29; and

R³ is chosen from the group consisting of phosphatidic acid, phosphatidyl choline, phosphatidyl glycerol and phosphatidyl serine; and

(b) at least one phospholipid with covalently linked polymers or polysaccharides.

72. (Withdrawn) A liposomal drug delivery system for administering an active lysolipid drug substance, which is not a substrate for lysophospholipase, to tissues expressing increased levels of extracellular phospholipase A2, comprising:

(a) a prodrug lipid derivative having the formula:



wherein

X and Z are O;

Y is -OC(O)-, Y then being connected to R² via either the oxygen or carbonyl carbon atom;

R¹ and R² are each independently an alkyl group (CH₂)_nCH₃, where n is any one of 11-29; and

R³ is chosen from the group consisting of phosphatidic acid, phosphatidyl choline, phosphatidyl glycerol and phosphatidyl serine; and

(b) at least one phospholipid with covalently linked polymers or polysaccharides.

73. – 74. (Cancelled)

75. (New) The method according to claim 16, wherein said mammal is a human.